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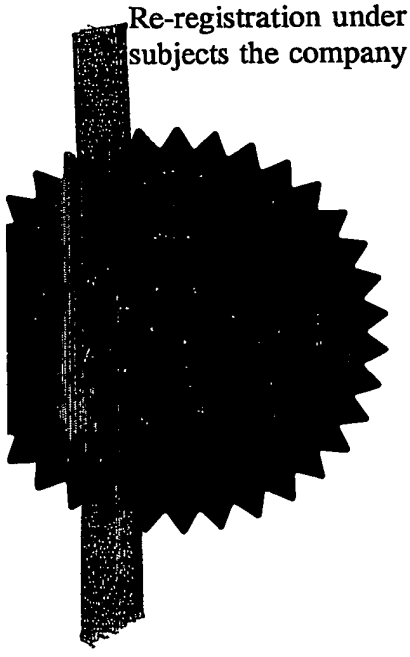

CERTIFIED COPY OF PRIORITY DOCUMENT

Signed Stephen Hordley

Dated 25 September 2003

Patents Form 1/77

E753849-2 D02029
P01/[illegible]00 0.00-0223236.1

Patents Act 1977
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The Patent Office

1/77

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Request for grant of a patent

(See the notes on the back of this form. You can also get an explanatory leaflet from the Patent Office to help you fill in this form)

The Patent Office

Cardiff Road
Newport
Gwent NP9 1RH

1.	Your Reference	**DMK/P33122**
2.	Patent application number *(The Patent office will fill in this part)*	0223236.1
3.	Full name, address and postcode of the or of each applicant *(underline all surnames)*	**GLAXO GROUP LIMITED** **GLAXO WELLCOME HOUSE** **BERKELEY AVENUE** **GREENFORD** **MIDDLESEX** **UB6 ONN** **GB**
	Patents ADP number *(if you know it)*	07357003
	If the applicant is a corporate body, give the country/state of its corporation	**GB**
4	Title of the invention	**COMPOUNDS**
5	Name of your agent *(if you know one)*	**DENISE MCKINNELL**
	"Address for service" in the United Kingdom to which all correspondence should be sent *(including the postcode)*	**GLAXOSMITHKLINE** **CORPORATE INTELLECTUAL PROPERTY** **CN925.1** **980 GREAT WEST ROAD** **BRENTFORD** **MIDDLESEX** **TW8 9GS, GB**
	Patents ADP number *(if you know it)*	80725550 06

		Country	Priority application number *(if you know it)*	Date of Filing (day / month / year)
6.	If you are declaring priority from one or more earlier patent applications, give the country and date of filing of the or of each of these earlier applications and *(if you know it)* the or each application number			

		Number of earlier application	Date of filing (day / month / year)
7.	If this application is divided or otherwise derived from an earlier UK application, give the number and the filing date of the earlier application		

8.	Is a statement of inventorship and of right to grant a patent required in support of this request? *(Answer yes if:* *a) any applicant named in part 3 is not an inventor, or* *b) there is an inventor who is not named as an applicant, or* *c) any named applicant is a corporate body.*	**YES**

See note (d))

Patents Form 1/77

9. (Enter the number of sheets for any of the following items you are filing with this form. Do not count copies of the same document

Continuation sheets of this form	-
Description	12
Claim(s)	2
Abstract	
Drawing(s)	

10. If you are also filing any of the following, state how many against each item

Priority Documents	
Translations of priority documents	
Statement of inventorship and right to grant of a patent *(Patents Form 7/77)*	
Request for preliminary examination and search *(Patent Form 9/77)*	
Request for substantive examination *(Patent Form 10/77)*	
Any other documents *(please specify)*	

11. **I/~~We~~ request the grant of a patent on the basis of this application**

DMcKinnell **Signature DENISE MCKINNELL. 7 October 2002**
AGENT FOR THE APPLICANTS

12. Name and daytime telephone number of person to contact in the United Kingdom

JEAN HARNEY
020 8047 4420

Warning

After an application for a patent has been filed, the Comptroller of the Patent Office will consider whether publication of communication of the invention should be prohibited or restricted under Section 22 of the Patents Act 1977. You will be informed if it is necessary to prohibit or restrict your invention in this way. Furthermore, if you live in the United Kingdom, Section 23 of the patent Act 1977 stops you from applying for a patent abroad without first getting written permission form the Patent Office unless an application has been filed at least 6 weeks beforehand in the United Kingdom for a patent for the same invention and either no direction prohibiting publication or communication has been given, or any such direction has been received

a) *Notes*

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b) *Write your answers in capital letters using black ink or you may type them.*

c) *If there is not enough space for all the relevant details on any part of this form, please continue on a separate sheet of paper and write "see continuation sheet" in the relevant part(s). Any continuation sheet should be attached to this form*

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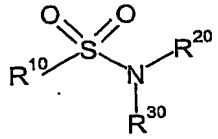
Compounds

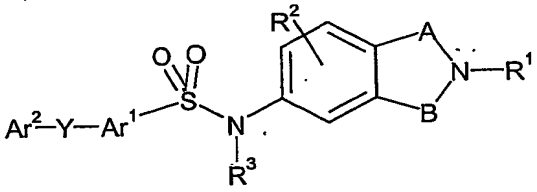
This invention relates to novel compounds, pharmaceutical compositions containing them and their use in therapy, in particular as antipsychotic agents.

US patent number US 5,684,195 discloses a method of preparing sulfonamides of the formula



wherein R^{10} represents, *inter alia*, an optionally substituted 5- or 6-membered heteroaryl, R^{20} represents, *inter alia*, tetrahydroisoquinolinyl and R^{30} represents, *inter alia*, hydrogen or C_{1-6}alkyl. In US 5,684,195, it is stated that sulfonamides in general have been widely used for the treatment of bacterial or viral infections and are also found in drugs such as diuretics, hypoglycemic, antimalarial agents amongst others.

According to the invention, there is provided a compound of formula (I):



(I)

wherein

A and B represent the groups $-(CH_2)_m-$ and $-(CH_2)_n-$ respectively;

R^1 represents C_{1-6}alkyl;

R^2 represents hydrogen, halogen, hydroxy, cyano, nitro, hydroxyC_{1-6}alkyl, trifluoromethyl, trifluoromethoxy, C_{1-6}alkyl, C_{1-6}alkoxy, $-(CH_2)_pC_{3-6}$cycloalkyl, $-(CH_2)_pOC_{3-6}$cycloalkyl, $-COC_{1-6}$alkyl, $-SO_2C_{1-6}$alkyl, $-SOC_{1-6}$alkyl, $-S-C_{1-6}$alkyl, $-CO_2C_{1-6}$alkyl, $-CO_2NR^4R^5$, $-SO_2NR^4R^5$, $-(CH_2)_pNR^4R^5$, $-(CH_2)_pNR^4COR^5$, an optionally substituted aryl group, an optionally substituted heteroaryl group or an optionally substituted heterocyclyl group;

R^3 represents hydrogen or C_{1-6}alkyl;

Ar^1 represents an optionally substituted heteroaryl group;

Ar^2 represents an optionally substituted phenyl or an optionally substituted heteroaryl group;

Y represents a bond, -O-, $-C_{1-6}$alkyl-, $-CR^6R^7X-$, $-XCR^6R^7-$, $-NR^8CO-$ or $-CONR^8-$;

X represents oxygen, sulfur, -SO- or $-SO_2-$;

R^4 and R^5 each independently represent hydrogen or C_{1-6}alkyl or, together with the nitrogen or other atoms to which they are attached, form an azacycloalkyl ring or an oxo-substituted azacycloalkyl ring;

R^6 and R^7 each independently represent hydrogen, C_{1-6}alkyl or fluoro;

R^8 represents hydrogen or C_{1-6}alkyl;

m and n independently represent an integer selected from 1 and 2 with the proviso that m and n cannot both represent 2;

p independently represents an integer selected from 0, 1, 2 and 3;

or a pharmaceutically acceptable derivative thereof.

In a first aspect of the invention, there is provided a compound of the formula (I) as defined above with the proviso that when m represents 1 and n represents 2 or m represents 2 and n represents 1 and R^2 represents halogen, C_{1-6}alkyl or C_{1-6}alkoxy, Y is other than a bond.

It is to be understood that the present invention covers all combinations of particular and preferred groups described herein above.

As used herein, the term "alkyl", either alone or as part of another group, refers to straight or branched hydrocarbon chains containing the specified number of carbon atoms. For example, C_{1-6}alkyl means a straight or branched alkyl containing at least 1, and at most 6, carbon atoms. Examples of "alkyl" as used herein include, but are not limited to, methyl, ethyl, n-propyl, n-butyl, n-pentyl, n-hexyl, isobutyl, isopropyl, t-butyl and 1,1-dimethylpropyl.

As used herein, the term "alkoxy" refers to a straight or branched alkoxy group containing the specified number of carbon atoms. For example, C_{1-6}alkoxy means a straight or branched alkoxy group containing at least 1, and at most 6, carbon atoms. Examples of "alkoxy" as used herein include, but are not limited to, methoxy, ethoxy, propoxy, prop-2-oxy, butoxy, but-2-oxy, 2-methylprop-1-oxy, 2-methylprop-2-oxy, pentoxy or hexyloxy.

As used herein, the term "cycloalkyl" refers to a non-aromatic hydrocarbon ring containing the specified number of carbon atoms. For example, C_{3-7}cycloalkyl means a non-aromatic ring containing at least three, and at most seven, ring carbon atoms. Examples of "cycloalkyl" as used herein include, but are not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl. A C_{6-7}cycloalkyl group is preferred.

As used herein, the term "halogen" refers to the elements fluorine, chlorine, bromine and iodine. Preferred halogens are fluorine, chlorine and bromine.

As used herein, the term "aryl" refers to a phenyl or a naphthyl ring.

As used herein, the term "heteroaryl" refers to a 5- or 6-membered heterocyclic aromatic ring or a fused bicyclic heteroaromatic ring system.

As used herein, the term "heterocyclyl" refers to a 3- to 7-membered monocyclic saturated ring containing at least one heteroatom independently selected from oxygen, nitrogen and sulfur. Examples of suitable heterocyclic rings include, but are not limited to, piperidine and morpholine.

As used herein, the term "5- or 6-membered heterocyclic aromatic ring" refers to a monocyclic unsaturated ring containing at least one heteroatom independently selected from oxygen, nitrogen and sulfur. Examples of suitable 5- and 6-membered heterocyclic aromatic rings include, but are not limited to, furyl, thienyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, oxadiazolyl, thiadiazolyl, pyridyl, triazolyl, triazinyl, pyridazyl, pyrimidinyl, pyrazolyl, isothiazolyl and isoxazolyl.

As used herein, the term "fused bicyclic heteroaromatic ring system" refers to a ring system comprising one six-membered unsaturated ring and one 5- or 5-membered unsaturated rig fused together, the ring system containing at least one heteroatom independently selected from oxygen, nitrogen and sulfur. Examples of suitable fused bicyclic heteroaromatic ring systems include, but are not limited to, indolyl, indolinyl, benzofuranyl, benzothienyl, quinolyl, isoquinolyl, tetrahydroquinolyl, benzodioxanyl, indanyl and tetrahydronapthyl.

As used herein, the term "azacycloalkyl ring" refers to a 4- to 7-membered monocyclic saturated ring containing one nitrogen atom. Examples of suitable azacycloalkyl rings are azetidine, pyrrolidine, piperidine and azepine.

As used herein, the term "oxo-substituted azacycloalkyl ring" refers to an azacycloalkyl ring as defined above substituted by one oxo group. Examples of suitable oxo-substituted azacycloalkyl rings include, but are not limited to, azetidinone, pyrrolidinone, piperidinone and azepinone.

As used herein, the term "optionally substituted" refers to optional substitution with the named substituent or substituents, multiple degrees of substitution being allowed unless otherwise stated.

As used herein "pharmaceutically acceptable derivative" includes any pharmaceutically acceptable salt, solvate, ester or salt of such ester of a compound of formula (I) which, upon administration to the recipient is capable of providing (directly or indirectly) a compound of formula (I) or an active metabolic or residue thereof.

As used herein, the term "solvate" refers to a complex of variable stoichiometry formed by a solute (in this invention, a compound of formula (I) or a salt thereof) and a solvent. Such solvents for the purpose of the invention may not interfere with the biological activity of the solute. Examples of suitable solvents include water, methanol, ethanol and acetic acid. Most preferably the solvent used is water and the solvate may also be referred to as a hydrate.

It will be appreciated that for use in medicine the salts of formula (I) should be pharmaceutically acceptable. Suitable pharmaceutically acceptable salts will be apparent to those skilled in the art and include for example acid addition salts formed with inorganic acids e.g. hydrochloric, hydrobromic, sulfuric, nitric or phosphoric acid; and organic acids e.g. succinic, maleic, malic, mandelic, acetic, fumaric, glutamic, lactic, citric, tartaric, benzoic, benzenesulfonic, p-toluenesulfonic, methanesulfonic or naphthalenesulfonic acid. Other non-physiologically acceptable salts e.g. oxalates, may be used, for example in the isolation of compounds of formula (I) and are included within the scope of this invention. Also included within the scope of the invention are solvates and hydrates of the compounds of formula (I).

Certain of the compounds of formula (I) may form acid addition salts with one or more equivalents of the acid. The present invention includes within its scope all possible stoichiometric and non-stoichiometric forms thereof.

Certain compounds of formula (I) may exist in stereoisomeric forms (e.g. they may contain one or more asymmetric carbon atoms). The individual stereoisomers (enantiomers and diastereomers) and mixtures of these are included within the scope of the present invention. The present invention also covers the individual isomers of the compounds represented by formula (I) as mixtures with isomers thereof in which one or more chiral centres are inverted. Likewise, it is understood that compounds of formula (I) may exist in tautomeric forms other than that shown in the formula and these are also included within the scope of the present invention.

Preferably, R^1 represents C_{1-4}alkyl. More preferably, R^1 represents methyl, ethyl, n-propyl or isopropyl. Even more preferably, R^1 represents methyl.

The group R^2 may be located at any free position on its respective phenyl ring.

When R^2 represents an optionally substituted aryl group, an optionally substituted heteroaryl group or an optionally substituted heterocyclyl group, the optional substituents may be independently selected from C_{1-6}alkyl, C_{1-6}alkoxy, halogen, trifluoromethyl, trifluoromethoxy, cyano and –S-C_{1-6}alkyl. Preferably, the optional substituents are independently selected from chloro, fluoro, bromo, methyl, ethyl, t-butyl, methoxy, trifluoromethyl, trifluoromethoxy, cyano and –S-methyl.

Preferably, R^2 represents hydrogen, halogen, C_{1-6}alkyl or C_{1-6}alkoxy. More preferably, R^2 represents hydrogen, halogen, C_{1-4}alkyl or C_{1-4}alkoxy. Even more preferably, R^2 represents hydrogen or methoxy.

Preferably, R^3 represents hydrogen or C_{1-4}alkyl. More preferably, R^3 represents hydrogen, methyl, ethyl, n-propyl or isopropyl. Even more preferably, R^3 represents hydrogen.

When Ar^1 represents an optionally substituted heteroaryl group, the optional substituents may be independently selected from C_{1-6}alkyl, C_{1-6}alkoxy, halogen, trifluoromethyl, trifluoromethoxy, cyano and –S-C_{1-6}alkyl. Preferably, the optional substituents are independently selected from chloro, fluoro, methyl, methoxy, trifluoromethyl and trifluoromethoxy.

Preferably, Ar^1 is substituted by 0 to 3 substituents, more preferably 0, 1 or 2 substituents. Preferably, Ar^1 represents optionally substituted thienyl.

Preferably, Ar^1 represents optionally substituted thienyl whereby one or more optional substituents are selected from halogen (such as chloro, e.g. 4-chloro, or fluoro, e.g. 4-fluoro, 2,4-difluoro or 3,4-difluoro), C_{1-6}alkyl (such as methyl, e.g. 2-methyl), C_{1-6}alkoxy (such as methoxy, e.g. 3-methoxy or 4-methoxy), trifluoromethyl (e.g.3-trifluoromethyl or 4-trifluoromethyl) and trifluoromethoxy. Other examples of multiple optional substituents include, for example, 2-methyl-4-chloro. Even more preferably, Ar^1 represents unsubstituted thienyl.

When Ar^2 represents optionally substituted phenyl or an optionally substituted heteroaryl group, the optional substituents may be independently selected from C_{1-6}alkyl, C_{1-6}alkoxy, halogen, trifluoromethyl, trifluoromethoxy, cyano and –S-C_{1-6}alkyl. Preferably, the optional substituents are independently selected from chloro, fluoro, methyl, methoxy, trifluoromethyl and trifluoromethoxy.

Preferably, Ar^2 is substituted by 0 to 3 substituents, more preferably 1 or 2 substituents.

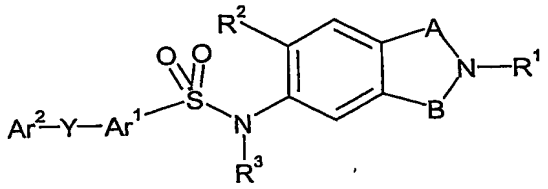
Preferably, Ar^2 represents optionally substituted phenyl, isoxazolyl, thiazolyl or thienyl. More preferably, Ar^2 represents optionally substituted phenyl.

Preferably, Ar^2 represents optionally substituted phenyl whereby one or more optional substituents are selected from halogen (such as chloro, e.g. 4-chloro, or fluoro, e.g. 4-fluoro, 2,4-difluoro or 3,4-difluoro), C_{1-6}alkoxy (such as methoxy, e.g. 3-methoxy or 4-methoxy), trifluoromethyl (e.g.3-trifluoromethyl or 4-trifluoromethyl) and trifluoromethoxy or Ar^2 represents optionally substituted thiazolyl whereby one or more optional substituents are selected from C_{1-6}alkyl (such as methyl, e.g. 2-methyl).

Preferably, R^4 and R^5 independently represent hydrogen or C_{1-4}alkyl. More preferably, R^4 and R^5 independently represent hydrogen or methyl.

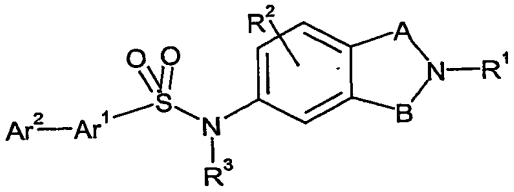
Preferably, R^6 and R^7 independently represent hydrogen, fluoro or methyl. More preferably, R^6 and R^7 independently represent hydrogen.

Preferably, R^8 represents hydrogen or methyl. More preferably, R^8 represents hydrogen.
Preferably, p represents 0.
In a further aspect of the invention, there is provided a compound of formula (IA):



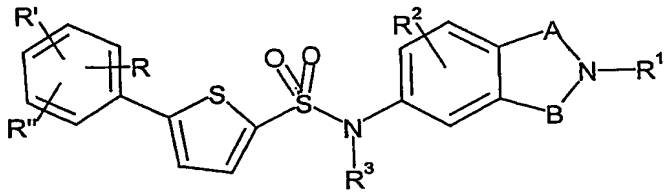
(IA)

or a pharmaceutically acceptable derivative thereof wherein groups A, B, Ar^1, Ar^2, Y and R^1 to R^3 have any of the meanings as given hereinbefore. For compounds of formula (IA), R^2 is preferably hydrogen or methoxy.
In a further aspect of the invention, there is provided a compound of the formula (IA) as defined above with the proviso that when m represents 1 and n represents 2 or m represents 2 and n represents 1 and R^2 represents halogen, C_{1-6}alkyl or C_{1-6}alkoxy, Y is other than a bond.
In a further aspect of the invention, there is provided a compound of formula (IB):



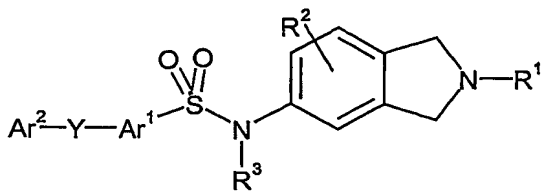
(IB)

or a pharmaceutically acceptable derivative thereof wherein groups A, B, Ar^1, Ar^2 and R^1 to R^3 have any of the meanings as given hereinbefore.
In a further aspect of the invention, there is provided a compound of the formula (IB) as defined above with the proviso that when m represents 1 and n represents 2 or m represents 2 and n represents 1 and R^2 represents halogen, C_{1-6}alkyl or C_{1-6}alkoxy, Y is other than a bond.
In a further aspect of the invention, there is provided a compound of formula (IC):



(IC)

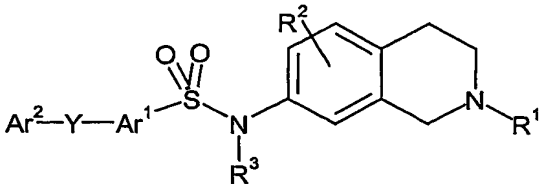
or a pharmaceutically acceptable derivative thereof wherein groups A, B and R^1 to R^3 have any of the meanings as given hereinbefore and the groups R, R′ and R″ represent up to three optional substituents on the phenyl ring as defined hereinbefore for the group Ar^2.
In a further aspect of the invention, there is provided a compound of the formula (IC) as defined above with the proviso that when m represents 1 and n represents 2 or m represents 2 and n represents 1 and R^2 represents halogen, C_{1-6}alkyl or C_{1-6}alkoxy, Y is other than a bond.
In a further aspect of the invention, there is provided a compound of formula (ID):



(ID)

or a pharmaceutically acceptable derivative thereof wherein groups Ar^1, Ar^2, Y and R^1 to R^3 have any of the meanings as given hereinbefore.

In a further aspect of the invention, there is provided a compound of formula (IE):

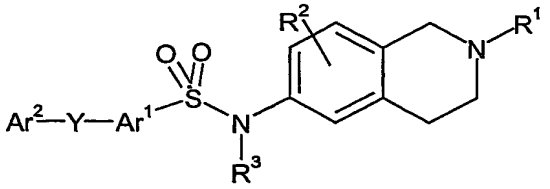


(IE)

or a pharmaceutically acceptable derivative thereof wherein groups Ar^1, Ar^2, Y and R^1 to R^3 have any of the meanings as given hereinbefore.

In a further aspect of the invention, there is provided a compound of the formula (IE) as defined above with the proviso that when m represents 1 and n represents 2 or m represents 2 and n represents 1 and R^2 represents halogen, C_{1-6}alkyl or C_{1-6}alkoxy, Y is other than a bond.

In another aspect of the invention, there is provided a compound of formula (IF):



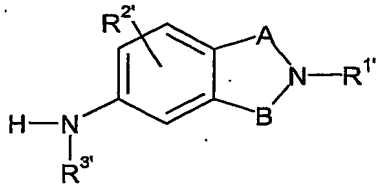
(IF)

or a pharmaceutically acceptable derivative thereof wherein groups Ar^1, Ar^2, Y and R^1 to R^3 have any of the meanings as given hereinbefore.

In a further aspect of the invention, there is provided a compound of the formula (IF) as defined above with the proviso that when m represents 1 and n represents 2 or m represents 2 and n represents 1 and R^2 represents halogen, C_{1-6}alkyl or C_{1-6}alkoxy, Y is other than a bond.

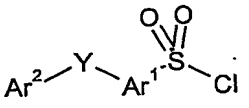
The present invention also provides a general process (A) for preparing compounds of formula (I) which process comprises:

reacting a compound of formula (II)



(II)

with a compound of formula (III)



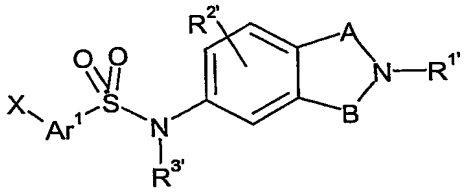
(III)

wherein A, B, Ar^1, Ar^2 and Y are as hereinbefore defined and $R^{1'}$-$R^{3'}$ represent R^1 to R^3 as hereinbefore defined or are groups that may be readily convertible to R^1 to R^3.

This general method (A) can be conveniently performed by mixing the two components in a solvent such as pyridine or dichloromethane (in the presence of a base), at 0°C.

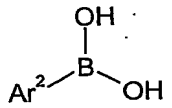
The present invention also provides a general process (B) for preparing compounds of formula (I) wherein Y is a bond, which process comprises:

reacting a compound of formula (IV)



(IV)

with an aryl boronic acid of formula (V)

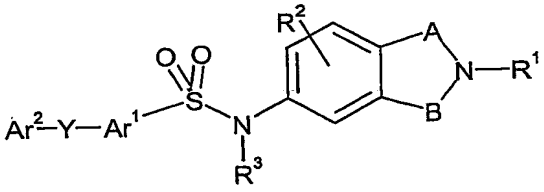


(V)

wherein X is a leaving group, such as iodo, bromo or triflate, A, B, Ar^1 and Ar^2 are as hereinbefore defined and $R^{1'}$-$R^{3'}$ represent R^1 to R^3 as hereinbefore defined or are groups that may be readily convertible to R^1 to R^3, under standard Suzuki conditions, e.g. treatment of compound (IV) with 4-chlorobenzeneboronic acid in toluene containing aqueous sodium carbonate and a catalytic amount of Pd $(PPh_3)_4$, at reflux under argon.

The present invention also provides a general process (C) for preparing compounds of formula (I) which process comprises:

converting a compound of formula (I)



(I)

wherein A, B, Ar^1, Ar^2, Y and R^1 to R^3 are as hereinbefore defined, into another compound of formula (I) by substituting the group R^1 or the group R^3 using conventional techniques.

Interconversion of one of the $R^{1'}$ to $R^{3'}$ group to the corresponding R^1 to R^3 groups another typically arises when one compound of formula (I) is used as the immediate precursor of another compound of formula (I), or when it is easier to introduce a more complex or reactive substituent at the end of a synthetic sequence.

For example, conversion of $R^{1'}$ from a t-butoxycarbonyl (BOC) group to hydrogen is conducted by the treatment of the N-BOC protected compound with hydrogen chloride in ethanol or dioxan at room temperature.

Conversion of $R^{1'}$ from hydrogen to an alkyl group is conducted by the treatment of the sulfonamide NH compound with the appropriate aldehyde in dichloroethane in the presence of a reducing agent, such as sodium triacetoxyborohydride, or by the treatment of the NH compound with the appropriate alkyl halide, such as iodomethane, under standard alkylation conditions (potassium carbonate in DMF at 60°C).

Conversion of $R^{3'}$ from hydrogen to an alkyl group is conducted by the treatment of the sulfonamide NH compound with the appropriate alcohol, such as methanol, under Mitsunobu conditions i.e. treatment with diisopropyl azodicarboxylate/triphenylphosphine and methanol in tetrahydrofuran at room temperature.

Compounds of formula (II) are known in the literature or may be prepared by known processes, for example, reduction of the corresponding nitro compound as disclosed in WO 99/14197, or by procedures analogous to these procedures. Suitable examples of an $R^{1'}$ protecting group are trifluoroacetyl or the t-butoxycarbonyl (BOC) group.

Compounds of formula (III) are commercially available or may be prepared by established procedures, for example chlorosulfonylation of a suitable substituted aromatic precursor, using chlorosulfonic acid, for example as described in J. Med. Chem., 2000, 43, 156-166.

Compounds of formula (IV) may be prepared from compounds of formula (II) by the treatment with the appropriate heteroaryl sulfonyl chloride using standard conditions, for example in pyridine or dichloromethane in the presence of a base such as triethylamine at room temperature.

Compounds of formula (V) are commercially available or may be prepared by known methodology, for example lithiation of a suitable substituted bromoheteroaryl at low temperature followed by quenching with tri-isopropylborate and acidic hydrolysis of the reaction product.

Compounds of formula (I) have been found to exhibit affinity for dopamine receptors, in particular the D_3 and D_2 receptors, and are useful in the treatment of disease states which require modulation of such receptors, such as psychotic conditions. Many of the compounds of formula (I) have also been found to have greater affinity for dopamine D_3 than for D_2 receptors. The therapeutic effect of currently available antipsychotic agents (neuroleptics) is generally believed to be exerted via blockade of D_2 receptors; however this mechanism is also thought to be responsible for undesirable extrapyramidal side effects (eps) associated with many neuroleptic agents. Without wishing to be bound by theory, it has been suggested that blockade of the dopamine D_3 receptor may give rise to beneficial antipsychotic activity without significant eps. (see for example Sokoloff et al, Nature, 1990; 347: 146-151; and Schwartz et al, Clinical Neuropharmacology, Vol 16, No. 4, 295-314, 1993). Additionally, certain compounds of formula (I) have antagonist affinity for the serotonin 5-HT_{2A}, 5-HT_{2C} and 5-HT_6 receptors. These additional properties may give rise to enhanced anti-psychotic activity (e.g. improved effects on cognitive dysfunction) and/or reduced eps.

The compounds of formula (I) are of use as antipsychotic agents for example in the treatment of schizophrenia, schizo-affective disorders, psychotic depression, mania, paranoid and

delusional disorders. Furthermore, they could have utility as adjunct therapy in Parkinsons Disease, particularly with compounds such as L-DOPA and possibly dopaminergic agonists, to reduce the side effects experienced with these treatments on long term use (e.g. see Schwartz et al., Brain Res. Reviews, 1998, 26, 236-242). From the localisation of D_3 receptors, it could also be envisaged that the compounds could also have utility for the treatment of substance abuse where it has been suggested that D3 receptors are involved (e.g. see Levant, 1997, Pharmacol. Rev., 49, 231-252). Examples of such substance abuse include alcohol, cocaine, heroin and nicotine abuse. Other conditions which may be treated by the compounds include dyskinetic disorders such as Parkinson's disease, neuroleptic-induced parkinsonism and tardive dyskinesias; depression; anxiety, cognitive impairment including memory disorders such as Alzheimers disease, eating disorders, obesity, sexual dysfunction, sleep disorders, emesis, movement disorders, obsessive-compulsive disorders, amnesia, aggression, autism, vertigo, dementia, circadian rhythm disorders and gastric motility disorders e.g. IBS.

The invention also provides the use of a compound of formula (I) or a pharmaceutically acceptable derivative thereof in therapy.

The invention also provides a compound of formula (I) or a pharmaceutically acceptable derivative thereof for use in the treatment of a condition in a mammal for which modulation (especially antagonism/inhibition) of dopamine receptors (especially dopamine D_3 receptors) and/or serotonin receptors (especially 5-HT_6, 5-HT_{2A} and 5-HT_{2C}) is beneficial.

A preferred use for dopamine/serotonin antagonists according to the present invention is in the treatment of psychoses such as schizophrenia or in the treatment of substance abuse.

Therefore, also provided is a compound of formula (I) or a pharmaceutically acceptable derivative thereof for use in the treatment of a psychotic condition (e.g. schizophrenia) or substance abuse in a mammal.

The invention also provides the use of a compound of formula (I) or a pharmaceutically acceptable derivative thereof in the manufacture of a medicament for the treatment of a condition in a mammal for which modulation (especially antagonism/inhibition) of dopamine receptors (especially dopamine D_3 receptors) and/or serotonin receptors (especially 5-HT_6, $5HT_{2A}$ and 5-HT_{2C}) is beneficial.

Also provided is the use of a compound of formula (I) or a pharmaceutically acceptable derivative thereof in the manufacture of a medicament for the treatment of a psychotic condition (e.g. schizophrenia) or substance abuse in a mammal.

In a further aspect therefore the present invention provides a method of treating a condition for which modulation (especially antagonism/inhibition) of dopamine receptors (especially dopamine D_3 receptors) and/or serotonin receptors (especially 5-HT_6, $5HT_{2A}$ and 5-HT_{2C}) is beneficial, which comprises administering to a mammal (e.g. human) in need thereof an effective amount of a compound of formula (I) or a pharmaceutically (i.e. physiologically) acceptable derivative thereof. Such conditions in particular include psychoses/psychotic conditions such as schizophrenia, and substance abuse.

Thus, a still further aspect the invention provides a method of treating a psychotic condition (e.g. schizophrenia) or substance abuse which comprises administering to a mammal (e.g.

human) in need thereof an effective amount of a compound of formula (I) as herein defined or a pharmaceutically acceptable derivative thereof.

Also provided is a compound of formula (I) or a pharmaceutically acceptable derivative thereof for use as an active therapeutic substance in a mammal, e.g. for use in the treatment of any of the conditions described herein.

"Treatment" includes prophylaxis, where this is appropriate for the relevant condition(s).

For use in medicine, the compounds of the present invention are usually administered as a standard pharmaceutical composition. The present invention therefore provides in a further aspect a pharmaceutical composition comprising a compound of formula (I) or a pharmaceutically (i.e. physiologically) acceptable derivative thereof and a pharmaceutically (i.e. physiologically) acceptable carrier. The pharmaceutical composition can be for use in the treatment of any of the conditions described herein.

The compounds of formula (I) may be administered by any convenient method, for example by oral, parenteral (e.g. intravenous), buccal, sublingual, nasal, rectal or transdermal administration and the pharmaceutical compositions adapted accordingly.

The compounds of formula (I) and their pharmaceutically acceptable derivatives which are active when given orally can be formulated as liquids or solids, for example syrups, suspensions or emulsions, tablets, capsules and lozenges.

A liquid formulation will generally consist of a suspension or solution of the compound or pharmaceutically acceptable derivative in a suitable liquid carrier(s) for example an aqueous solvent such as water, ethanol or glycerine, or a non-aqueous solvent, such as polyethylene glycol or an oil. The formulation may also contain a suspending agent, preservative, flavouring or colouring agent.

A composition in the form of a tablet can be prepared using any suitable pharmaceutical carrier(s) routinely used for preparing solid formulations. Examples of such carriers include magnesium stearate, starch, lactose, sucrose and cellulose.

A composition in the form of a capsule can be prepared using routine encapsulation procedures. For example, pellets containing the active ingredient can be prepared using standard carriers and then filled into a hard gelatin capsule; alternatively, a dispersion or suspension can be prepared using any suitable pharmaceutical carrier(s), for example aqueous gums, celluloses, silicates or oils and the dispersion or suspension then filled into a soft gelatin capsule.

Typical parenteral compositions consist of a solution or suspension of the compound or pharmaceutically acceptable derivative in a sterile aqueous carrier or parenterally acceptable oil, for example polyethylene glycol, polyvinyl pyrrolidone, lecithin, arachis oil or sesame oil. Alternatively, the solution can be lyophilised and then reconstituted with a suitable solvent just prior to administration.

Compositions for nasal administration may conveniently be formulated as aerosols, drops, gels and powders. Aerosol formulations typically comprise a solution or fine suspension of the active substance in a pharmaceutically acceptable aqueous or non-aqueous solvent and are usually presented in single or multidose quantities in sterile form in a sealed container, which can take the form of a cartridge or refill for use with an atomising device. Alternatively the sealed container may be a unitary dispensing device such as a single dose nasal inhaler or an

aerosol dispenser fitted with a metering valve which is intended for disposal once the contents of the container have been exhausted. Where the dosage form comprises an aerosol dispenser, it will contain a propellant which can be a compressed gas such as compressed air or an organic propellant such as a fluorochlorohydrocarbon. The aerosol dosage forms can also take the form of a pump-atomiser.

Compositions suitable for buccal or sublingual administration include tablets, lozenges and pastilles, wherein the active ingredient is formulated with a carrier such as sugar and acacia, tragacanth, or gelatin and glycerin.

Compositions for rectal administration are conveniently in the form of suppositories containing a conventional suppository base such as cocoa butter.

Compositions suitable for transdermal administration include ointments, gels and patches.

Preferably the composition is in unit dose form such as a tablet, capsule or ampoule.

Each dosage unit for oral administration contains preferably from 1 to 250 mg (and for parenteral administration contains preferably from 0.1 to 25 mg) of a compound of the formula (I) or a pharmaceutically acceptable derivative thereof calculated as the free base.

The pharmaceutically acceptable compounds of the invention will normally be administered in a daily dosage regimen (for an adult patient) of, for example, an oral dose of between 1 mg and 500 mg, preferably between 10 mg and 400 mg, e.g. between 10 and 250 mg or an intravenous, subcutaneous, or intramuscular dose of between 0.1 mg and 100 mg, preferably between 0.1 mg and 50 mg, e.g. between 1 and 25 mg of the compound of the formula (I) or a pharmaceutically acceptable derivative thereof calculated as the free base, the compound being administered 1 to 4 times per day. Suitably the compounds will be administered for a period of continuous therapy, for example for a week or more.

Biological Test Methods

Binding experiments on cloned dopamine (e.g. D2 and D3) receptors

The ability of the compounds to bind selectively to human D2/D3 dopamine receptors can be demonstrated by measuring their binding to cloned receptors. The inhibition constants (K_i) of test compounds for displacement of [^{125}I]-Iodosulpride binding to human D2/D3 receptors expressed in CHO cells were determined as follows. The cell lines were shown to be free from bacterial, fungal and mycoplasmal contaminants, and stocks of each were stored frozen in liquid nitrogen. Cultures were grown as monolayers or in suspension in standard cell culture media. Cells were recovered by scraping (from monolayers) or by centrifugation (from suspension cultures), and were washed two or three times by suspension in phosphate buffered saline followed by collection by centrifugation. Cell pellets were stored frozen at -80°C. Crude cell membranes were prepared by homogenisation followed by high-speed centrifugation, and characterisation of cloned receptors achieved by radioligand binding.

Preparation of CHO cell membranes: Cell pellets were gently thawed at room temperature, and resuspended in about 20 volumes of ice-cold Extraction buffer; 5mM EDTA, 50mM Trizma pre-set crystals (pH7.4@37°C), 1mM $MgCl_2$, 5mM KCl and 120mM NaCl. The suspension was homogenised using an Ultra-Turrax at full speed for 15 seconds. The homogenate was centrifuged at 18,000 r.p.m for 15 min at 4°C in a Sorvall RC5C centrifuge. Supernatant was discarded, and homogenate re-suspended in extraction buffer then

centrifugation was repeated. The final pellet was resuspended in 50mM Trizma pre-set crystals (pH 7.4 @ 37°C) and stored in 1ml aliquot tubes at –80°C (D2 = 3.0E+08 cells, D3 = 7.0E+07 cells and D4 = 1.0E+08 cells). The protein content was determined using a BCA protocol and bovine serum albumin as a standard (Smith, P. K., et al., Measurement of protein using bicinchoninic acid. Anal. Biochem. 150, 76-85 (1985)).

Binding experiments: Crude D2/D3 cell membranes were incubated with 0.03nM [^{125}I]-Iodosulpride (~2000 Ci/mmol; Amersham, U. K., and the test compound in a buffer containing 50mM Trizma pre-set crystals (pH 7.4 @ 37°C), 120mM NaCl, 5mM KCl, 2mM $CaCl_2$, 1mM $MgCl_2$, 0.3% (w/v) bovine serum albumin. The total volume is 0.2ml and incubated in a water bath at 37°C for 40 minutes. Following incubation, samples were filtered onto GF/B Unifilters using a Canberra Packard Filtermate, and washed four times with ice-cold 50mM Trizma pre-set crystals (pH 7.4 @ 37°C). The radioactivity on the filters was measured using a Canberra Packard Topcount Scintillation counter. Non-specific binding was defined with 10μM SKF-102161 (YM-09151). For competition curves, 10 serial log concentrations of competing cold drug were used (Dilution range: 10μM-10pM). Competition curves were analysed using Inflexion, an iterative curve fitting programme in Excel. Results were expressed as pK_i values where

$pK_i = -\log10[Ki]$.

Binding experiments on cloned 5-HT_6 receptors

Compounds can be tested following the procedures outlined in WO 98/27081.

Binding experiments on cloned 5-HT_{2C} receptors

Compounds can be tested following the procedures outlined in WO 94/04533 and *British Journal of Pharmacology* (1996) **117**, 427-434.

Binding experiments on cloned 5-HT_{2A} receptors

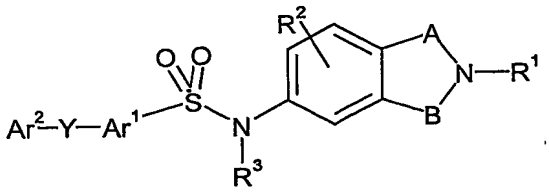
Compounds can be tested following the procedures outlined in *British Journal of Pharmacology* (1996) **117**, 427-434.

All publications, including but not limited to patents and patent applications, cited in this specification are herein incorporated by reference as if each individual publication were specifically and individually indicated to be incorporated by reference herein as though fully set forth.

The application of which this description and claims forms part may be used as a basis for priority in respect of any subsequent application. The claims of such subsequent application may be directed to any feature or combination of features described herein. They may take the form of product, composition, process or use claims and may include, by way of example and without limitation, one or more of the following claims:

Claims

1. A compound of formula (I)



(I)

wherein

A and B represent the groups $-(CH_2)_m-$ and $-(CH_2)_n-$ respectively;

R^1 represents C_{1-6}alkyl;

R^2 represents hydrogen, halogen, hydroxy, cyano, nitro, hydroxyC_{1-6}alkyl, trifluoromethyl, trifluoromethoxy, C_{1-6}alkyl, C_{1-6}alkoxy, $-(CH_2)_pC_{3-6}$cycloalkyl, $-(CH_2)_pOC_{3-6}$cycloalkyl, $-COC_{1-6}$alkyl, $-SO_2C_{1-6}$alkyl, $-SOC_{1-6}$alkyl, $-S-C_{1-6}$alkyl, $-CO_2C_{1-6}$alkyl, $-CO_2NR^4R^5$, $-SO_2NR^4R^5$, $-(CH_2)_pNR^4R^5$, $-(CH_2)_pNR^4COR^5$, an optionally substituted aryl group, an optionally substituted heteroaryl group or an optionally substituted heterocyclyl group;

R^3 represents hydrogen or C_{1-6}alkyl;

Ar^1 represents an optionally substituted heteroaryl group;

Ar^2 represents an optionally substituted phenyl or an optionally substituted heteroaryl group;

Y represents a bond, -O-, $-C_{1-6}$alkylene-, $-CR^6R^7X-$, $-XCR^6R^7-$, $-NR^8CO-$ or $-CONR^8-$;

X represents oxygen, sulfur, -SO- or $-SO_2-$;

R^4 and R^5 each independently represent hydrogen or C_{1-6}alkyl or, together with the nitrogen or other atoms to which they are attached, form an azacycloalkyl ring or an oxo-substituted azacycloalkyl ring;

R^6 and R^7 each independently represent hydrogen, C_{1-6}alkyl or fluoro;

R^8 represents hydrogen or C_{1-6}alkyl;

m and n independently represent an integer selected from 1 and 2 with the proviso that m and n cannot both represent 2;

p independently represents an integer selected from 0, 1, 2 and 3;

or a pharmaceutically acceptable derivative thereof.

2. A compound of formula (I) according to claim 1 wherein R^1 represents methyl.

3. A compound of formula (I) according to claim 1 or claim 2 wherein R^2 represents hydrogen, halogen, C_{1-6}alkyl or C_{1-6}alkoxy.

4. A compound of formula (I) according to any of claims 1 to 3 wherein R^3 represents hydrogen.

5. A compound of formula (I) according to any of claims 1 to 4 wherein Ar^1 represents optionally substituted thienyl.

6. A compound of formula (I) according to any of claims 1 to 5 wherein Ar^2 represents optionally substituted phenyl, isoxazolyl, thiazolyl and thienyl.

7. A pharmaceutical composition comprising a compound of formula (I) as claimed in any of claims 1 to 6 or a pharmaceutically acceptable derivative thereof and a pharmaceutically acceptable carrier therefor.

8. Use of a compound of formula (I) according to any of claims 1 to 6 or a pharmaceutically acceptable derivative thereof in therapy.

9. Use of a compound of formula (I) according to any of claims 1 to 6 for the treatment of a condition which requires modulation of a dopamine receptor.

10. Use of a compound of formula (I) according to claim 9 wherein the condition is schizophrenia or substance abuse.

11. Use of a compound of formula (I) according to any of claims 1 to 6 in the manufacture of a medicament for the treatment of a condition which requires modulation of a dopamine receptor.

12. Use of a compound of formula (I) according to claim 9 wherein the condition is schizophrenia or substance abuse.

13. A method of treating a condition which requires modulation of dopamine receptors which comprises administering to a mammal in need thereof an effective amount of a compound of formula (I) according to any of claims 1 to 6.

14. A method of treating a condition according to claim 13 wherein the condition is schizophrenia or substance abuse.